# Dietary Carotene and Vitamin A and Risk of Lung Cancer Among White Men in New Jersey [1]

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ABSTRACT—A population-based incident case-control study of lung cancer in white males was conducted during 1980-81 in six high-risk areas of New Jersey. Interviews were completed with 763 cases and 900 controls or with their next of kin. In order to assess whether dietary intake of carotene, preformed retinol, or total vitamin A modified the risk of lung cancer, subjects were asked about their usual frequency of consumption, several years earlier, of 44 food items, which provide 83% of the vitamin A in the American diet, and about their use of vitamin supplements. The men in the lowest quartile of carotene intake had 1.3 the risk (*P*-value for trend = .05) of those in the highest quartile after adjustment was made for smoking duration and intensity and education. No association was seen for retinol (*P*-value for trend = .11) or total vitamin A (*P*-value for trend = .30). The inverse association between carotene intake and lung cancer was most compelling for squamous cell carcinoma, with the smoking- and education-adjusted risk of those in the lowest quartile reaching 1.4 (*P*-value for trend =.03) the risk of those men in the highest quartile. Risk of lung adenocarcinoma was not related to carotene intake. The reduction in risk of squamous cell lung cancer with increasing carotene intake was noted in pipe and cigar smokers and cigarette smokers of different intensities. Among nonsmokers adenocarcinoma predominated. The inverse association between carotene and risk of squamous cell lung cancer was not especially strong or graded in response; but it was consistent and could be noted in each stratum when the subjects were divided by education, age, or mode of interview (direct vs. next of kin). The results of the other 4 case-control and 3 cohort studies that have looked at diet and risk of lung cancer are not consistent, and the question whether dietary carotene or total vitamin A reduces the risk of lung cancer is not yet resolved.—JNCI 1984; 73:1429-1435.

Both vitamin A and carotene have been proposed to reduce the risk of cancer in general and of epithelial and lung cancers in particular. Carotene is a precursor of vitamin A and occurs in plant foods. Vitamin A activity is also derived from retinol, an active form of the vitamin occurring in animal foods.

The vitamin A hypothesis evolved first. An acknowledged physiologic role for vitamin A is the regulation of cell differentiation. Because cancer is characterized by uncontrolled cell differentiation, inadequate vitamin A possibly may be related to the development of cancer. Since the mid 1960's, numerous animal experiments have demonstrated that pharmacologic doses of retinol and retinoids (synthetic chemical analogs of retinol) can retard or prevent the growth of tumors (*1*). The tumors had been induced by a variety of agents at a number of different sites. Whether physiologically normal variation in vitamin A intake affects carcinogenesis in animals is not clear.

β-Carotene and several other carotenoids synthesized by plants can be metabolized to vitamin A in humans. The conversion of carotene to vitamin A is not reversible. In 1981, Peto et al. (*2*) proposed that the intake of β-carotene might reduce, through one of several mechanisms, the risk of cancer. Carotene, or a metabolite, might be involved in cell differentiation like the retinoids; or it might function via an immunologic mechanism. Carotene might capture free radicals, just as it does in photosynthesis, and thus protect lipids and/or DNA from oxidative degradation (*3, 4*).

In 1980 we designed a large case-control study of lung cancer in the high-risk areas of New Jersey to assess the roles of smoking, occupation, and other potential risk factors. Several prospective cohort (*5, 6*) and case-control studies (*7, 8*) had reported inverse relationships between consumption of vitamin A sources and risk of lung cancer, yet none had evaluated the independent contributions of total vitamin A and carotene to the relationship. We appended to our interview a dietary section that included most of the major sources of vitamin A so that we could distinguish the two hypotheses.

## METHODS

A population-based incident case-control study of male lung cancer was implemented in six clusters of New Jersey municipalities with unusually high lung cancer mortality rates for white males during 1967-76. Cases were men, 25-89 years of age, who had been diagnosed as having primary cancer of the lung, trachea, or bronchus

ABBREVIATIONS USED: CI=confidence interval; NOS=not otherwise specified; RR=relative risk(s).

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between September 1, 1980, and October 31, 1981, and who were resident in these six high-risk areas of New Jersey. Cases were ascertained through a rapid reporting system the New Jersey State Health Department had established with local hospitals and by periodic review of hospital pathology records. Additional cases were identified with New Jersey cancer registry and death certificate files. Pathology reports, and other medical records as necessary, were reviewed by Health Department physicians to verify diagnosis. Only histologically confirmed cases of primary lung cancer were included in the study.

An approximately equivalent number of controls was selected in one of two ways: For those cases directly interviewed, controls were randomly selected from New Jersey licensed drivers and were frequency matched to cases within strata of age (5-yr intervals), race, and high-risk area of residence. For those cases for whom surrogates had to be interviewed, either because the case had died or was incapacitated, controls were selected from the New Jersey mortality files and individually matched to cases by age, race, high-risk area of residence, and year of death.

This analysis has been restricted to white males, including Hispanics, because black males are still being ascertained to obtain larger numbers. Of the 1,084 white cases identified for the study and 1,422 controls selected for them, 763 (70%) and 900 (63%), respectively, were successfully interviewed. Reasons for nonresponse are reported in detail elsewhere (*9*).

The interview included questions about tobacco use, occupational history, exposure to certain materials, residential history, medical history, demographic background, and diet. Diet was assessed by means of questions about the usual frequency of consumption, approximately 4 years earlier, of the 44 food items listed in table 1. Included were the major sources of preformed retinol (dairy products, eggs, liver, and fortified cereals) and carotene (selected fruits, vegetables, and juices). Certain food items, such as hot red chili peppers and guacamole, were incorporated because a parallel case-control study of lung cancer along the Texas Gulf Coast was to use the same questionnaire. For fruits and vegetables that the respondent said were eaten primarily in certain seasons, questions were asked about frequency of consumption both in season and out of season and the length of season. Vitamin A supplementation was assessed through questions about the type(s) of vitamins used and the duration and usual intensity of use.

The average frequency of consumption over an entire year was calculated for each food item. Nutrient intake was calculated as the weighted sum of the yearly frequencies of consumption of the food items containing that nutrient, with the weights being the nutrient contents of typical portions of the food items (*10, 11*). Typical portion sizes for white adult males were approximated on the basis of two recent national nutrition surveys (*12, 13*). Because of the limited number of food items included in the questionnaire, only the intake of carotene, preformed retinol, and total vitamin A could be reliably calculated. We arrived at definitions of low (L), moderate (M), and high (H) levels of consumption of each nutrient by splitting the frequency distribution of the control population at the 25th and 75th percentiles.

Total vitamin A intake was calculated in two ways from the intake of retinol and carotene. The first was according to the 1966 World Health Organization convention (*14*), whereby retinol was assumed to be twice as active as an equivalent weight of carotene because of inefficient metabolic conversion of carotene to retinol in humans. The second was according to the 1980 National Academy of Sciences convention (*15*), whereby retinol was assumed to be six times as active as an equivalent weight of carotene because of inefficient conversion and because animal experiments had indicated that carotene

TABLE 1.—*Food items in questionnaire*[a]

| Sources of preformed retinol | Sources of carotene | |
|---|---|---|
| 1. Eggs | 1. Prunes or prune juice | 17. Summer squash (s) |
| 2. Milk on cereal | 2. Tomato or V-8 juice | 18. Winter squash (s) |
| 3. Milk | 3. Grapefruit juice | 19. Sweet potato or pumpkin (s) |
| 4. Cottage cheese or yogurt | 4. Cooked tomatoes or tomato sauce | 20. Broccoli (s) |
| 5. Cheese | 5. Corn torillas, cornbread, grits | 21. Greens, such as spinach, turnip greens, collards (s) |
| 6. Cheese in a combination dish such as lasagna, pizza | 6. Fresh tomato (s) | 22. Cantaloupe (s) |
| 7. Ice cream | 7. Head lettuce (s) | 23. Watermelon (s) |
| 8. Butter or margarine | 8. Green cabbage or coleslaw (s) | 24. Fresh peaches (s) |
| 9. Chicken liver | 9. Leaf lettuce (s) | 25. Canned peaches (s) |
| 10. Beef or calves liver | 10. Carrots (s) | 26. Nectarines (s) |
| 11. Cold cereal (s) | 11. Carrots in a salad or stew or mixed with other vegetables (s) | 27. Apricots (s) |
| 12. Super-fortified cold cereal (s) | 12. Green beans (s) | 28. Pink grapefruit (s) |
| 13. Instant breakfast, breakfast squares, or toaster tarts (s) | 13. Green peas (s) | 29. Sweet green pepper (s) |
| | 14. Asparagus (s) | 30. Sweet red pepper (s) |
| | 15. Avocado or guacamole (s) | 31. Hot red chili peppers or hot pepper sauce (s) |
| | 16. Corn (s) | |

[a] (s) implies that the respondent was asked whether the food was eaten during the entire year, primarily in certain seasons, or not at all.

was more poorly absorbed through the intestines than was previously thought.

Occasionally, respondents would not know whether a food item had been eaten or, if eaten, how often, or the details of the seasonality of consumption. Those 25 individuals (1.5% of study subjects) for whom nonquantitative responses were noted for 5 or more food items were eliminated from the dietary analysis. For the remaining 1,638 study subjects (750 cases and 888 controls), the responses were quantitative for 99.8% of the food items. In calculating nutrient intake, appropriate medians were substituted for any nonquantitative responses. For example, the median level of consumption of a food item within the entire population was introduced when it had not been ascertained whether the food item had been eaten. The median level of consumption for those individuals who actually had eaten the food was introduced when it was known that the food had been eaten but not how often.

Of the 1,638 study subjects, 990 (60%) were directly interviewed. The 648 surrogate interviews were with wives (67%), children (21%), siblings (9%), or other relatives (4%).

The effect of diet on lung cancer risk was measured by maximum likelihood estimates of the RR, adjusted, if necessary, for confounding variables by stratification into multiple contingency tables (*16*). Mantel's extension test (*17*) was used to test the progressive dependence (trend) of the RR on decreasing levels of nutrient intake. Logistic regression with case-control status as the dependent variable (*18*) was used to confirm the results derived by stratified analysis.

## RESULTS

The smoking-adjusted RR of lung cancer for decreasing intake of preformed retinol, carotene, and vitamin A are shown in table 2. Only with carotene was there a statistically significant trend of increasing risk with decreased nutrient intake, with those individuals in the lowest quartile of consumption having 1.3 (95% CI= 0.9-1.8) the risk of those in the highest quartile. No inverse association between total vitamin A intake or retinol intake and risk of lung cancer could be detected. A clear gradient in risk with carotene intake was not apparent, nor did comparison of extremes (the lowest and highest deciles of carotene consumers) enhance the smoking-adjusted RR obtained by comparison of the lowest and highest quartiles of carotene consumers.

Adjustment for smoking reduced the crude RR for those individuals in the lowest quartile of carotene intake, relative to those in the highest quartile of intake, from 1.5 to 1.3. To control for smoking, we divided the study subjects into six strata: 1) nonsmokers, 2) pipe and cigar smokers only, 3) cigarette smokers of low intensity (<25 cigarettes/day) and low duration (≤40 yr), 4) cigarette smokers of low intensity and high duration, 5) cigarette smokers of high intensity and low duration, and 6) cigarette smokers of high intensity and high duration. No additional reduction of the RR for carotene intake was noted when the cigarette intensity and duration strata were divided more finely, when total number of pack-years was used, or when years since cigarette smoking ceased was considered. No additional reduction in risk was noted when the smoking-adjusted RR for carotene were also controlled for education. No additional confounding was seen when the smoking-adjusted RR were controlled for exposure to high-risk jobs or to high-risk materials, mode of interview (with subject or surrogate), age, or high-risk area of residence. High-risk occupations and materials were empirically defined as those for which the smoking-adjusted RR was ≥1.5 in this study population.

TABLE 2.—*Smoking-adjusted RR of lung cancer for retinol, carotene, and vitamin A intake*

| Nutrient | Level of consumption | | | *P*-value for trend |
|---|---|---|---|---|
| | Upper 25% | Middle 50% | Lower 25% | |
| Retinol | 1.0 | 1.0 | 0.8 | .11 |
| Carotene | 1.0 | 1.3 | 1.3 | .05 |
| Vitamin A (1966 definition) | 1.0 | 0.9 | 1.1 | .30 |
| Vitamin A (1980 definition) | 1.0 | 1.0 | 0.9 | .30 |

Table 3 shows the smoking-adjusted RR of lung cancer by histologic type for decreasing levels of carotene intake. For squamous cell carcinoma, which comprised 49% of the cases, a gradient in risk was seen, with the RR of the lowest quartile of carotene consumers reaching 1.4 (95% CI=1.0-2.1) that of the highest quartile. However, for adenocarcinoma (16% of the cases), no increase in risk with decreasing carotene intake was noted. For small cell or oat cell carcinoma (15% of the cases), risk seemed increased with decreased carotene intake, but no clear gradient was seen. The same finding was true for miscellaneous cell types grouped together: undifferentiated and anaplastic, large cell, and adenosquamous carcinomas. Carcinoma NOS, probably containing many uncharacterized squamous cell carcinomas, was inversely associated with carotene intake. Smoking was controlled as described for table 2.

When the relationship of total vitamin A intake or retinol intake to the smoking-adjusted RR of lung cancer was examined by cell type—squamous cell carcinoma, small cell carcinoma, and adenocarcinoma—no statistically significant associations were observed.

The smoking-adjusted RR of squamous cell lung cancer for decreasing intake of retinol, carotene, and vitamin A are shown in table 4. Only with carotene was there a statistically significant trend. No significant dose-response relationships with retinol or vitamin A intake were noted. The gradient in RR noted for carotene intake did not continue at all levels of exposure; when the lowest decile of carotene consumers was compared to the highest decile, the smoking-adjusted RR, although unstable, was only 1.3.

RR for squamous cell lung cancer in table 4 were adjusted for smoking in the same manner as were the overall lung cancer RR in table 2. No further reduction

TABLE 3.—*Smoking-adjusted RR for carotene intake, by histologic type of lung cancer*

| Lung cancer | | Level of consumption | | | *P*-value for trend |
|---|---|---|---|---|---|
| Cell type | No. of cases | Upper 25% | Middle 50% | Lower 25% | |
| Squamous | 364 | 1.0 | 1.3 | 1.4 | .03 |
| Small cell | 113 | 1.0 | 1.7 | 1.3 | .28 |
| Adenocarcinoma | 118 | 1.0 | 0.9 | 0.8 | .24 |
| Other[a] | 84 | 1.0 | 1.9 | 1.3 | .26 |
| NOS | 62 | 1.0 | 1.3 | 2.1 | .03 |

[a] Other cell types include undifferentiated and anaplastic (57), large cell (21), and adenosquamous (6) carcinomas.

in the RR for carotene intake was noted when the RR were adjusted for finer cuts of cigarette smoking duration, finer cuts of cigarette smoking intensity, pack-years, or years since smoking had ceased. No additional reduction in the smoking-adjusted RR for carotene was noted when the RR were concurrently controlled for education. Also, no additional confounding was seen when the smoking-adjusted RR were controlled for exposure to high-risk jobs or high-risk materials, mode of interview, age, or high-risk area of residence.

The increase in risk of squamous cell lung cancer associated with decreased carotene intake was noted for both cigarette smokers and for pipe and cigar smokers. Only 4 cases with squamous cell histology had never smoked; therefore, we were unable to assess the impact of carotene intake in nonsmokers with squamous cell lung cancer. The inverse association with carotene intake was visible in cigarette smokers who had smoked $<20$, 20-29, or $\geq 30$ cigarettes a day and in those who had smoked for 31-45 or $>45$ years. The inverse association with carotene intake was not noted in smokers of $\leq 30$ years' duration nor in smokers who had stopped smoking $>10$ years ago. These interactions are being investigated further.

Whether the study sample was stratified by age, by education level, or by mode of interview (subject or surrogate), the increase in risk of squamous cell lung cancer associated with decreased carotene intake was seen in each stratum, even after adjustment for smoking.

## DISCUSSION

The dietary component of this case-control study of lung cancer among white men in New Jersey was designed to distinguish whether intake of carotene or total vitamin A modifies the risk of lung cancer. The food items included in the interview questionnaire provide 83% of the vitamin A in the U.S. diet, according to data collected in the second U.S. Health and Nutrition Examination Study, 1976-80 (*19*). Carotene intake was inversely associated with risk of lung cancer. Preformed retinol intake was not related to risk, nor was total vitamin A intake related to risk. The contribution of carotene-containing foods to vitamin A activity in the diets of New Jersey white men was not substantial enough for the carotene-lung cancer association to be reflected in a vitamin A-lung cancer association, whether the carotene contribution to vitamin A activity was calculated by the 1966 convention or by the less generous 1980 convention. This finding is not surprising. According to the 1977-78 U.S. Department of Agriculture Food Consumption Survey (*20*), the usual foods available to the U.S. consumer provide 45% of total vitamin A activity as carotene if the 1966 convention is applied and 21% as carotene if the 1980 convention is applied.

The smoking-adjusted risk of lung cancer for those in the lowest quartile of carotene intake was only 1.3 that of those in the highest quartile. The inverse association between carotene and lung cancer was most evident for squamous cell carcinoma. Lung adenocarcinoma did not seem related to carotene intake. Risk of small cell carcinoma and undifferentiated, large cell, and adenosquamous carcinoma combined seemed somewhat increased with decreased carotene intake.

The reduction in risk of squamous cell lung cancer with increasing carotene intake was noted in pipe and cigar smokers and in cigarette smokers of different intensities. Among nonsmokers the relationship of carotene to risk of squamous cell lung cancer could not be evaluated because of small numbers. However, adenocarcinoma was the most common cell type among the nonsmokers with lung cancer, accounting for 5 of 13 cases; and risk of adenocarcinoma was unrelated to carotene intake.

The data still are being analyzed. The relationship of the intake of various food groups, such as vegetables and fruit, to risk of lung cancer is being assessed. The role of vitamin supplements containing vitamin A is being examined. Also, the apparent absence of an inverse association between carotene consumption and squamous cell lung cancer among smokers of short smoking duration and ex-smokers is being pursued.

The inverse relationship between carotene intake and risk of lung cancer, although statistically significant, was not strong even when only squamous cell carcinomas were considered. The risk of squamous cell lung cancer for those in the lowest quartile of carotene intake only reached 1.4 that of those in the highest quartile, and the RR did not show a persuasive dose-response relationship. However, the inverse association between carotene and squamous cell lung cancer was consistent. It was noted in the subjects directly interviewed and in those interviewed via surrogates, among subjects of different ages, and among subjects of different educational attainment. In

TABLE 4.—*Smoking-adjusted RR of squamous cell lung cancer for retinol, carotene, and vitamin A intake*

| Nutrient | Level of consumption | | | *P*-value for trend |
|---|---|---|---|---|
| | Upper 25% | Middle 50% | Lower 25% | |
| Retinol | 1.0 | 1.1 | 1.0 | .47 |
| Carotene | 1.0 | 1.3 | 1.4 | .04 |
| Vitamin A (1966 definition) | 1.0 | 1.0 | 1.2 | .09 |
| Vitamin A (1980 definition) | 1.0 | 1.1 | 1.1 | .34 |

addition, the association was specific. Intake of carotene, but not of retinol, was related to risk of lung cancer. The association was noted for squamous cell carcinoma but not for adenocarcinoma.

The inverse association between carotene intake and risk of squamous cell lung cancer may be stronger than it appears because of the imprecision involved in measuring carotene intake and the resultant instability of the estimated RR. Certainly, it is difficult for people to recall precisely their usual frequency of consumption of a number of food items several years earlier. Questions on usual portion size were not asked, and typical portion sizes, derived from national surveys, were assumed for all individuals in the study. Even the carotene contents for the various food items have limited accuracy. Vitamin A values listed in the U.S. Department of Agriculture food composition tables (*10*), from which carotene values were derived for vegetables and fruit, were determined by different assay techniques performed by different laboratories in different decades and were sometimes imputed from findings for similar foods. The assay method most often used measured not only β-carotene but also other carotenoids (both active and inactive) and their isomers and esters, and it measured each carotenoid with a different efficiency unrelated to its efficacy in cancer prevention (*21*). In particular, if β-carotene alone, or some other specific carotenoid, were uniquely responsible for the reduction in cancer risk, then the carotene contents derived from the food composition tables would have generated an imprecise estimate of the true exposure.

Three explanations other than causality may account for statistical associations: confounding, bias, and chance. Smoking was a confounder of the lung cancer-carotene relationship but was controlled with increasingly fine stratifications of smoking intensity, duration, pack-years, or recency of use until there was no evidence of residual confounding. None of the other risk factors assessed were confounders. Even when we controlled for education, which was used to measure other aspects of socioeconomic status and life-style possibly correlated with diet, the carotene associations were not reduced.

Bias is always a concern in case-control studies of diet and cancer, because the disease itself may affect dietary patterns prior to clinical onset or may alter recall of usual diet. Thus respondents were asked to report their diet for 4 years earlier and to ignore any recent changes. The specificity of the association is perhaps the best argument against bias. It is difficult to imagine a bias in recall of carotene-containing foods but not of retinol-containing foods. It is also hard to envision a greater bias in dietary recall among those with squamous cell carcinoma than among those with adenocarcinoma.

Four other case-control studies and three cohort studies also have looked for relationships between diet and risk of lung cancer. Bjelke (*5*) in a prospective cohort study among Norwegian men that yielded 36 cases of lung cancer for analysis showed that an index of vitamin A intake, including a limited number of its plant and animal sources, was inversely associated with risk of lung cancer. The RR for "low" vitamin A consumers, as compared to that of "high" consumers, reached 2.6. In 1977 MacLennan et al. (*7*), in a hospital-based case-control study of lung cancer among Singapore Chinese with 233 male and female cases, found that the consumption of green vegetables was inversely associated with the incidence of lung cancer. The RR reached 2.2. In 1979 Hirayama (*6*), in a prospective cohort study among Japanese men and women that yielded 807 cases of lung cancer, showed that consumption of green-yellow vegetables was inversely associated with incidence of lung cancer. In both the MacLennan and Hirayama studies, consumption of certain vegetables high in carotene seemed protective, but the contribution of these specific vegetables to total carotene intake in Singapore and Japan was not presented, and the relationship of preformed retinol intake to lung cancer risk was not assessed.

In 1979 Mettlin et al. (*8*), in a hospital-based case-control study of lung cancer among white males in upstate New York with 292 cases, found that a vitamin A index, composed of a limited number of plant and animal sources of vitamin A, was inversely associated with risk of lung cancer. The RR in low consumers compared to high consumers was 1.7. Because both milk and carrots were consumed more frequently by the controls than by the cases, both the retinol and carotene components of vitamin A activity seemed to be protective. In 1980 Gregor et al. (*22*), in a hospital-based case-control study of lung cancer in London with 100 male and female cases, noted that a vitamin A index based on a limited number of food items was inversely associated with risk in men but not in women. Among the men the crude RR for low consumers, compared to high consumers, was 2.5. Consumption of vitamin pills and liver, both of which contain retinol, accounted for the relationship with vitamin A. Among women, low vitamin A consumers were at reduced risk.

In 1981 Shekelle et al. (*23*) were the first to form separate indices of carotene and retinol intake in an epidemiologic study of lung cancer and to assess independently the relationship of each to the RR. The original dietary interviews for the cohort had been lost, but a series of approximations and assumptions enabled them to perform the necessary calculations. For the 33 men who developed lung cancer, only carotene was inversely related to incidence, with the RR reaching 7 among consumers in the lowest quartile of carotene intake relative to those in the highest quartile. Soup was the component of the carotene index that seemed the most protective. In 1983 Kvale et al. (*24*) confirmed Bjelke's (*5*) earlier inverse association between dietary vitamin A and lung cancer incidence in an extended follow-up of the same cohort of Norwegian men, but this time the study also included women. Now 168 lung cancer cases had accrued. The RR in men reached 1.5 among low vitamin A consumers. A similar and even stronger pattern was noted among the females. The observation that vegetables and milk were the food groups most strongly associated with decreased incidence suggested

that both the carotene and retinol components of vitamin A were involved.

In 1984 Hinds et al. (*25*), in a population-based case-control study among the multiethnic population of Hawaii involving 364 cases of lung cancer, found that both carotene and total vitamin A were inversely associated with risk in males but not in females. The effect of preformed retinol intake was not assessed; therefore, it is difficult to judge whether the vitamin A association reflected only an underlying carotene association. Among men the RR for consumers in the lowest quartile compared to consumers in the highest quartile was 1.8 for vitamin A and 2.2 for carotene. In women the risk of lung cancer increased as vitamin A or carotene intake increased. Because the carotene and vitamin A hypotheses had been defined before the interview for this study was drafted, a much higher percentage of vitamin A sources was included than in the previous studies discussed.

These epidemiologic studies of diet and lung cancer are not entirely consistent. Inverse associations were noted more frequently (in six of seven studies) with indices of carotene intake or carotene-containing foods than with indices of preformed retinol or retinol-containing foods. However, the relationship with retinol was not always assessed. Specifically, one study (*23*) showed an inverse association with carotene intake but not with retinol, three studies (*6, 7, 25*) showed inverse associations with carotene or carotene-rich foods but did not investigate an association with retinol, two studies (*8, 24*) showed inverse associations with both carotene- and retinol-rich foods, and one study (*22*) showed an inverse association with retinol but not with carotene. Two of these studies (*22, 25*) found diametrically opposite effects in men and women and stressed the results in the males, and one study (*24*) found comparable effects in both sexes. Independent inverse associations with both carotene and retinol would suggest that total vitamin A is the protective factor. In U.S. diets and Western European diets, vitamin A activity is derived primarily from retinol-containing foods, and an inverse association with carotene does not imply a similar association with total vitamin A. However, in Singapore (*7*), Japan (*6*), and Hawaii (*25*), where three studies found inverse associations with carotene or carotene-rich foods but did not investigate retinol, it is probable, though not proved, that vitamin A activity is derived primarily from carotene-containing foods and that inverse associations exist with total vitamin A intake. From this perspective, six of the seven studies are consistent with the hypothesis that total vitamin A intake protects against cancer (*6–8, 22, 24, 25*).

The four cohort studies that searched for a relationship between serum vitamin A in stored blood samples and subsequent lung cancer incidence are not especially relevant. Two studies (*26, 27*) failed to find any association of serum vitamin A with cancer in general or with lung cancer in particular. One study (*28*) found serum vitamin A inversely related to lung cancer though not a level of statistical significance but not related to all cancer; and one study (*29*) found serum vitamin A inversely related to all cancer as well as to lung cancer. However, in adequately nourished populations, serum vitamin A levels are maintained within a narrow range by liver stores and do not reflect dietary intake of vitamin A (*30–32*). Nevertheless, serum carotene is believed to reflect recent intake of carotene. This premise has been demonstrated for carotene supplementation at levels five times the Recommended Dietary Allowance for vitamin A (*31*) and for the day-to-day variation characteristic of the U.S. diet (*32*). The one published cohort study (*27*) that assayed total carotene in the stored sera found that serum carotene was not related to subsequent incidence of cancer in general or of lung cancer in particular. However, preliminary analyses of three other cohort studies (*33–35*) indicated that in all three studies serum $\beta$-carotene, separated by high-performance liquid chromatography, was reduced among those individuals who ultimately developed lung cancer. Without a doubt, the measurement of serum carotene is more reliable than the assessment of dietary carotene. However, studies of the relationship of serum carotene to subsequent cancer outcome do not entirely resolve the issue or preclude the need for studies of dietary carotene. Although serum carotene levels reflect consumption of carotene-containing foods, they also may be responsive to other aspects of diet and metabolism.

Although a number of studies indicate that the consumption of either carotene or vitamin A is protective against lung cancer—and the associations are strong—upon close examination the results are not consistent. Our case-control study suggests that carotene, rather than total vitamin A, is associated with reduced risk of lung cancer, but the association is not strong. Our study is one of only two epidemiologic studies [the other is (*25*)] that were designed to include in the interviews with subjects most of the foods containing carotene and vitamin A. More well-designed studies are indicated to evaluate these two hypotheses and to quantify any resulting associations.

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